REMARKS

I. Amendments

Claims 39-58 have been canceled. Claims 59-71 have been added. The newly added claims do not add or constitute new matter. Support for the newly added claims may be found throughout the specification and originally filed claims. More particularly, support for the newly added claims may be found, for example, at page 13, line 33 through page 21, line 28, at page 21, line 29 through page 23, line 24, at page 57, line 8 through page 61, line 22, or at page 61, line 24 through page 62, line 27 of the instant specification.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, 59-71 are pending in the instant application.

II. Claim Objections

The Examiner objected to claim 40 under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to limit the subject matter of a previous claim. The Examiner asserts that it is unclear how a screening marker differs from a selection marker, and therefore claim 40 fails to limit the subject matter of parent claim 39. Applicants respectfully disagree. The definition and distinction between the terms "selectable marker" and "screening marker" are clearly set forth at, for example, page 9, line 54 through page 10, line 30, or at page 20, lines 18-26 of the instant specification. However, claim 40 has been canceled and the current claims do not recite the term "screening marker." Therefore the Examiner's objection is no longer relevant.

III. Claim Rejections

A. Rejection under 35 U.S.C. § 101

The Examiner has rejected claims 44-58 under 35 U.S.C. 35 U.S.C. § 101, because the claimed invention is allegedly not supported by either a specific asserted utility or a well established utility. Applicants respectfully traverse this rejection.

In rejecting these claims, the Examiner states that the specification fails to teach a specific use for the transgenic mouse comprising a disruption in a lymphoid specific GPCR gene exhibiting a phenotype comprising cellular infiltration in lung, pancreas, stomach or liver. More particularly, the Examiner states that the specification only teaches a method for identifying agents that modulate lymphoid specific GPCR expression or function, but does not teach a use for such agents. Further, the Examiner states that the skilled artisan would allegedly not know how to determine the expression or function of a gene that has already been knocked out. In addition, the Examiner states that, since the specification does not teach any disease associated with the disclosed phenotype, the skilled artisan would not know how to use the mouse as a model to treat diseases associated with a disruption in a lymphoid specific GPCR gene.

Applicants respectfully disagree with the Examiner's conclusions, and believe the rejection is improper. Applicants contend that the transgenic mice do have specific and credible utility, which utility has been disclosed in the instant specification and is well known in the art of gene targeting. The specification discloses various uses for the transgenic mice, such as, for example, screening for agents capable of modulating a phenotype associated with a disruption in the lymphoid specific GPCR gene. Applicants did not limit the usefulness of the phenotype those associated with a disease. Despite this, Applicants have disclosed that these mice exhibit a phenotype of cellular infiltration in various tissues, including lung, pancreas, stomach and liver. And, although according to the Examiner cellular infiltration may not be directly associated with a specific disease, it is well known in the art that cellular infiltration would be associated with disorders or conditions such as, for example, inflammation or malignancy of the tissues affected. It would clearly be useful and of value to those skilled in the art to identify agents capable of affecting a phenotype such as those claimed presently, or conditions or disorders associated with the claimed phenotypes. Thus, one skilled in the art would know how to use the transgenic mice exhibiting a phenotype of cellular infiltration to screen for agents which affect cellular infiltration.

With regard to the Examiner's assertion that the only utility disclosed for the transgenic mice is for identifying agents that modulate lymphoid specific GPCR expression or function, or as a model for disease associated with a disruption in the lymphoid specific GPCR, Applicants strongly disagree. Applicants refer the Examiner to the specification at, for example, page 5, line 26, through page 6, line 9, page 6, lines 19-29, page 27, lines 14-17, and page 27, lines 30-33, as

only a few examples of uses extending beyond what the Examiner has asserted as the sole disclosed utility of the transgenic mice. Applicants further assert that many uses of the mice would be well within the knowledge of a person skilled in the relevant art. Further, regarding the assertion by the Examiner that it is not known how to determine the expression or function of a gene that has been knocked out using the transgenic mice as claimed, Applicants refer the Examiner to page 27, lines 18-29, which discloses an example of such a method.

Applicants contend that the utility of the transgenic mice as claimed would be well established within the art for the reasons set forth above. As claims 44-58 have been cancelled, and the utility of the invention as recited in claims 59-69 has been established in the arguments above, the Applicants believe that the rejection under 35 U.S.C. § 101 is no longer relevant, and request withdrawal of the rejection.

B. Rejection under 35 U.S.C. § 112, first paragraph

1) The Examiner has also rejected claims 44-58 under 35 U.S.C. § 112, first paragraph, as not enabling one skilled in the art to use the claimed invention due to the alleged lack of a specific asserted utility or a well established utility as noted above. Applicants respectfully traverse the rejection.

In light of the cancellation of claims and the arguments set forth above in response to the utility rejection under 35 U.S.C. § 101, Applicants believe that a specific and credibly utility has been established for the invention as currently claimed. Therefore, this aspect of the rejection under 35 U.S.C. 35 U.S.C. § 112, first paragraph, is no longer relevant.

2) The Examiner has stated that, if the utility rejection is overcome, claims 44-58 stand rejected under 35 U.S.C. § 112, first paragraph, for the scope of enablement, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

Specifically, the Examiner states that the specification supports the enablement of a homozygous lymphoid specific GPCR gene knockout mouse that lacks production of functional lymphoid specific GPCR protein, wherein the mouse exhibits cellular infiltration in the lung, pancreas, stomach, or liver, a method of making said mouse by introducing the knockout construct into embryonic stem cells, selecting ES cells comprising lymphoid specific GPCR construct, introducing said ES cells into a blastocyst, and producing a transgenic knockout

mouse, it does not reasonably provide enablement for a transgenic mouse comprising any type of lymphoid specific GPCR disruption and a method of making said knockout mouse by introducing the knockout construct into any type of cell, or introducing ES cells directly into the pseudopregnant mouse. Applicants respectfully disagree, and believe that one skilled in the art would be able to practice the invention as claimed. However, in order to expedite prosecution of the instant application, Applicants have cancelled claims 44-58.

In view of the cancellation of claims 44-58, the Examiner's rejection of these claims under 35 U.S.C. § 112, first paragraph, is moot. Applicants, therefore, respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph. New claims 59-71 recite a transgenic mouse and method of making a transgenic mouse, and cells and tissues obtained from the transgenic mouse, wherein the transgenic mouse lacks production of functional lymphoid specific GPCR and exhibits the disclosed phenotype of cellular infiltration of lung, pancreatic, liver or stomach tissue. Additionally, these claims recite a method of producing said transgenic mouse which includes additional steps, including the step of introducing a construct into a murine embryonic stem cell. Applicants submit that new claims 59-71 fully meet the requirements and are patentable under 35 U.S.C. § 112, first paragraph.

C. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 39-45, 47, 49, 53 and 55-58 under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Applicants respectfully traverse this rejection.

With regard to claims 39-45, 47, 49, 53 and 55-58, the Examiner asserts that the term "cellular infiltration" renders the claims indefinite because the nature of the cells that infiltrate the recited organs is unknown. Applicants submit that it is well known in the art what types of cells are capable of cellular infiltration of the recited organs or tissues. One skilled in the art would know the nature of the cells referred to when using the term "cellular infiltration" in the context of cellular infiltration of tissues due to the disruption of the lymphoid specific GPCR gene. However, Applicants submit that the new claims clearly define the nature of the infiltrating cells, rendering the Examiner's rejection moot.

Regarding claims 39-42, the Examiner asserts that the term "selectable marker" renders the claims indefinite as it is unclear how a selectable marker protein can be inserted into a vector

construct. The Applicants disagree, and believe the specification has clearly defined and described the term and how it would be used in the targeting vector. Further, one skilled in the art would know how a selectable marker would be introduced into such a vector to form a targeting construct. However, as these claims have been canceled, and the newly added claims recite a selectable marker gene, this aspect of the rejection is no longer relevant.

As the Examiner's rejections under 35 U.S.C. § 112, second paragraph, are no longer relevant, Applicants respectfully request withdrawal of the rejection. Applicants submit that new claims 59-71 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

C. Rejection under 35 U.S.C. § 103

Claims 1-8 and 10 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Mansour *et al.*, 1988, *Nature,* 336(24):348-352 ("Mansour"), in view of Schweickart *et al.*, 1994, *Genomics,* 23: 643-650 ("Schweickart"). Applicants believe this rejection is intended to be in reference to claims 39-43 (see Office Action, page 2), in light of the prior cancellation of claims 1-8 and 10. Regardless, Applicants respectfully traverse the rejection.

Applicants submit that new claims 59-71 are non-obvious over the teachings of the references cited. The claimed invention relates to the *in vivo* mammalian characterization of lymphoid-specific GPCR genes and methods and compositions relating thereto, all of which are not obvious in view of the sole or combined teachings and disclosures of Mansour and Schweickart.

According to the Examiner, Mansour teaches a strategy for targeted disruption of the *hprt* and proto-oncogene *int-2* in mice embryonic stem cells, and subsequent generation of knockout mice. The disclosure of Mansour specifically relates to a general method for isolating embryonic stem cells containing a targeted mutation in an endogenous gene. More particularly, Mansour teaches the targeted disruption of the *hprt* gene and the proto-oncogene *int-2* in mouse embryonic stem cells by homologous recombination using targeting constructs specific for these genes.

Schweickart, as characterized by the Examiner, teaches the cloning of the human and mouse lymphoid-specific GPCR gene designated EBI1 (for Epstein-Barr induced 1), and provides the cloned coding sequence for this gene. Further, the Examiner asserts that Schweickart teaches that EBI1 is highly homologous to several members of the leukocyte

chemotactic peptide receptor family and that its expression is specific to lymphoid organs. Further, according to the Examiner, Schweickart teaches that EBI1 may play a role in lymphocyte growth, differentiation, activation, leukocyte trafficking, and in the extravasation of blood cells into sites of inflammation.

As a basis of the obviousness rejection under 35 U.S.C. § 103, the Examiner asserts that the ordinary artisan would have been motivated to knock out the function of lymphoid specific GPCR gene in a mouse, using the lymphoid specific GPCR construct, in order to study the role this gene plays in lymphocyte growth and regulation, as suggested by Schweickart. The Examiner further asserts that the ordinary artisan would have had a reasonable expectation of success because of the teachings of Mansour and Schweickart. The Applicant respectfully disagrees.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must meet three basic criteria:

1. there must be some motivation or suggestion to modify the reference or combine reference teachings;
2. there must be a reasonable expectation of success; and
3. the prior art references must teach or suggest all the claim limitations.

There is no teaching in Schweickart that suggests the desirability of knocking out the lymphoid specific GPCR gene. On page 8 of the Office Action, the Examiner cites Schweickart as suggesting that EBI1, specifically, is highly homologous to several members of the leukocyte chemotactic peptide receptor family and its expression is specific to lymphoid organs. The Examiner further cites Schweickart as disclosing that the receptor plays a role in lymphocyte growth, differentiation, activation, leukocyte trafficking, and in the extravasation of blood cells into sites of inflammation, as noted above.

The suggestions by Schweickart that the lymphoid specific GPCR is involved in lymphocyte growth, differentiation, activation, leukocyte trafficking, and in the extravasation of blood cells into sites of inflammation is not sufficient motivation to modify Schweickart or to combine Schweickart with Mansour to produce a lymphoid specific GPCR gene knockout construct and/or mouse and, thus, to establish a *prima facie* case of obviousness. The mere fact that a reference can be modified does not render the invention obvious unless the prior art also suggests the desirability of the modification. In the instant case, Schweickart does not, in any way, suggest the desirability of knocking out the lymphoid specific GPCR gene, even as a way to

further elucidate the role of the receptor in lymphocyte growth, differentiation, activation, leukocyte trafficking, and in the extravasation of blood cells into sites of inflammation.

The Examiner asserts that the ordinary artisan would have had a reasonable expectation of success because of the teachings of Mansour, who teaches a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Schweickart, who teaches the coding sequence of the mouse lymphoid specific GPCR EBI1 gene. However, when combining references, the Examiner must show some teaching, motivation or suggestion to combine the references. The mere fact that the references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. Further, the fact that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. Finally, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. In the instant case, there is no motivation to combine the teachings of Mansour with Schweickart to achieve the claimed invention. Mansour teaches a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a gene. There is no teaching or suggestion in Mansour as to the desirability of a targeted disruption of a lymphoid specific GPCR gene. Similarly, Schweickart teaches the coding sequence of the lymphoid specific GPCR EBI1 gene. However, there is no suggestion in Schweickart to create a targeted disruption of a lymphoid specific GPCR gene.

Finally, to establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. However, neither Mansour nor Schweickart, alone or in combination, teaches all of the limitations of the instant claims. For example, neither Mansour nor Schweickart teach or suggest a targeting construct capable of disrupting a lymphoid specific GPCR gene in a transgenic mouse, resulting in lack of production of functional lymphoid specific GPCR protein leading to a phenotype, particularly not a phenotype of cellular infiltration, which invention is the subject of the pending claims.

As the obviousness rejection is no longer relevant as a result of the cancellation of claims, and as new claims 59-71 are not obvious in view of the teachings of Mansour and Schweickart, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103 (a).

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-611.

Respectfully submitted,

Date: October 23, 2003

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SEP 26 2003

OFFICE OF PETITIONS

In re Application of :
Keith D. Allen et al :
Application No. 09/815,937 : ON PETITION
Filed: March 22, 2001 :
Attorney Docket No. R-611 :

This is a decision on the petition under 37 CFR 1.137(b), filed September 15, 2003, to revive the above-identified application.

The petition is **DISMISSED**.

Any request for reconsideration of this decision must be submitted within TWO (2) MONTHS from the mail date of this decision. Extensions of time under 37 CFR 1.136(a) are permitted. The reconsideration request should include a cover letter entitled "Renewed Petition under 37 CFR 1.137(b)." No additional fee is required with any renewed petition. Petitioner is advised that this is **not** a final agency action decision.

The above-identified application became abandoned for failure to reply in a timely manner to the non-final Office action mailed November 5, 2002, which set a shortened statutory period for reply of three (3) months. No extensions of time under the provisions of 37 CFR 1.136(a) were obtained. Accordingly, the above-identified application became abandoned on February 6, 2003.

A grantable petition to revive an abandoned application under 37 CFR 1.137(b) must be accompanied by: (1) the required reply (unless previously filed), which may met by the filing of a continuing application in a nonprovisional application abandoned for failure to prosecute, but must be the payment of the issue fee or any outstanding balance thereof in an application or patent, abandoned or lapsed for failure to pay the issue fee or any portion thereof; (2) the petition fee as set forth in 37 CFR 1.17(m); (3) a statement that the entire delay in filing the required reply from the due date for the reply until the filing of a grantable petition pursuant to 37 CFR 1.137(b) was unintentional; and (4) any terminal disclaimer (and fee as set forth in 37 CFR 1.20(d)). This petition lacks item (2) above.

As to item (2), on September 15, 2003, the Office of Finance attempted to withdraw the money from Deposit Account No. 50-1271. Unfortunately, there were insufficient funds in the Deposit Account.

It is not apparent whether the person signing the statement of unintentional delay was in a position to have firsthand or direct knowledge of the facts and circumstances of the delay at issue. Nevertheless, such statement is being treated as having been made as the result of a reasonable inquiry into the facts and circumstances of such delay. See 37 CFR 10.18(b) and Changes to Patent Practice and Procedure; Final Rule Notice, 62 Fed. Reg. 53131, 53178 (October 10, 1997), 1203 Off. Gaz. Pat. Office 63, 103 (October 21, 1997). In the event that such an inquiry has not been made, petitioner must make such an inquiry. If such inquiry results in the discovery that it is not correct that the entire delay in filing the required reply from the due date for the reply until the filing of a grantable petition pursuant to 37 CFR 1.137(b) was unintentional, petitioner must notify the Office.

There is no indication that the person signing the instant petition was ever given a power of attorney or authorization of agent to prosecute the above-identified application. If the person signing the instant petition desires to receive future correspondence regarding this application, the appropriate power of attorney or authorization of agent must be submitted. While a courtesy copy of this decision is being mailed to the person signing the instant petition, all future correspondence will be directed to the address of currently of record until such time as appropriate instructions are received to the contrary.

Further correspondence with respect to this matter should be addressed as follows:

By mail: Mail Stop PETITION
Commissioner for Patents
Post Office Box 1450
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By hand: Crystal Plaza Four, Suite 3C23
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By fax: (703) 308-6916
Attn: Office of Petitions

Telephone inquiries concerning this decision should be directed to Wan Laymon at (703) 306-5685.

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